

In the Specification:

Please replace paragraphs [0004] - [0008] with the following paragraphs. A marked-up version of the original paragraphs, showing the changes made thereto, is attached.

C | --[0004] Including the SBH method, when complementariness between an oligonucleotide and a sample DNA is examined, it is very difficult to call whether a hybrid was formed or not using one probe for one test item, since the stability of a hybrid differs sequence to sequence, and there is no perfect signal for calling the full complementariness. Science vol. 274 p.610-614, 1996 discloses a method for calling by comparing the signal intensity of a perfect match hybrid and the weaker intensities of one-base mismatch hybrids. In this method, 15-mer oligonucleotide probes, differing from each other only by one mismatching base at the center of the sequence, are prepared, and the fluorescence intensities of the hybrids of the probes are compared. When the intensity of the full matched hybrid is stronger than that of other hybrids by a predetermined rate, it is called positive.

[0005] Further, USP 5,733,729 discloses a method using a computer to differentiate a base sequence of a sample from a comparison of fluorescence intensities of obtained hybrids for more accurate calling.

[0006] However, the actual binding strength of a hybrid depends on the GC content etc., and difference of the fluorescence intensity between a full match hybrid and a one-base mismatch hybrid also varies in a considerable range depending on the sequence. Thus, a method for calling whether a sequence is fully complementary to a probe or not, using a 15 mer oligonucleotide probe to compare it with other three probes having one mismatched base at the center thereof, can provide more accuracy if each stability is evaluated theoretically or empirically before comparison.

[0007] In addition, accurate calling requires precise quantification of signals, and therefore, precision apparatuses such as a confocal laser microscope. Furthermore, in order to measure the fluorescence intensity of a hybrid of every probe and to determine the gene sequence by analyzing the data, a large-scale computer apparatus as well as a detection apparatus for reading the arrays are further required. Therefore, this is a big obstacle for ready use of the DNA array.

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cont.

[0008] On the other hand, gene diagnosis using such a DNA array may be used in group medical examination, individual gene examination or gene-polymorphism study. In such a case, however, the above described precise measurement and analysis are not always required, where a large amount of samples are rapidly treated at a low cost in order to find out varied samples concerning a specific item from a large number of normal samples. Further, the precision apparatus and analysis as described above will be expensive. Accordingly, a concept that screening of the presence or absence of a variation is first performed, and then, detailed examinations of the samples suspected of variation are carried out by screening, saving both time and cost.--

Please replace paragraph [0011] with the following paragraph. A marked-up copy of the original paragraph, showing the changes made thereto, is attached.

--[0011] According to one aspect of the present invention, there is provided a method for screening of the presence or absence of variation in a region of a nucleic acid comprising the steps of:

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- (a) preparing a test nucleic acid corresponding to the region;
- (b) preparing a probe having a base sequence fully complementary to a normal sequence of the region, and a plurality of probes each having at least one base not complementary to the normal sequence;

(c) fixing the probes in separate regions on a surface of a substrate to prepare a DNA array substrate;

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about.
(d) reacting the test nucleic acid with the probes on the DNA array substrate;

(e) measuring signals in each region totally where the signals are originated from respective hybrids formed between the test nucleic acid and one of the probes; and

(f) determining the presence or absence of mutation in the test nucleic acid comparing with a histogram pattern of signals of all regions obtained using a normal sample without variation.--

Please replace paragraph [0028] with the following paragraph. A marked-up copy of the original paragraph, showing the changes made thereto, is attached.

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--[0028] When these 64 probes are grouped into every eight probes in order of the fluorescence intensity obtained by hybridization with the normal nucleic acid (hereinafter "fluorescence intensity of a probe(s)" means expected intensity of a hybrid of the probe with a nucleic acid of normal sequence, if not otherwise stated), the total fluorescence intensity of the first group should be extremely high and the total fluorescence quantity of the sixth, seventh and eighth groups should be zero. Such classification by the fluorescence intensity may be performed empirically or theoretically through calculations.--

In the Claims:

Please cancel claims 9 and 19 without prejudice or disclaimer.